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# Aqueous Eye Drop Solubilizing Vitamin As
# [Bitamin A-rui Kayouka Suisei Tengaizai]

Misao Koide, et al.

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| INVENTORS | (72): | KOIDE, MISAO; AOSHIMA, SHUJI; YANNNO, YURIKO |
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[Claim(s)] /2*

[Claim 1] An aqueous eye drop solubilizing vitamin As which is characterized in that the aqueous formula of vitamin As solubilized with a nonionic surfactant is filled in a polyethylene terephthalate container blocking a wavelength of 380nm or less by adding a pigment or pigment and U-polymer.

[Detailed Description of the Invention]

[0001]

[Industrial Field of Application] The present invention relates to an aqueous eye drop solubilizing vitamin As. More precisely, it relates to an aqueous eye drop solubilizing stable vitamin As which can be used practically for a long period, filling a polyethylene container capable of shielding light wherein the vitamin As in the solution are not transferred.

[0002]

[Prior Art] Vitamin As, including vitamin A oil and vitamin A fatty acid esters, have the function to maintain normal vision and mucous membrane in humans and animals, and deficiency induces night blindness, corneal/conjunctival asteatosis and growth inhibition. Thus, they are substances that are indispensable to the eye. When an eye drop containing vitamin As that are useful to eyes is filled into a container, polyethylene terephthalate, polypropylene, polycarbonate, U-polymer and the like that are less permeable for the container are generally used as the container material. However, these materials are permeated by almost all light,

* Claim and paragraph numbers correspond to those in the foreign text.

including UV-rays, such that light cannot be blocked. Thus, the material is (1) stored in a dark place or (2) protected by a highly light shielding bag. It is very difficult to use vitamin As, which are very unstable against light, without interference with stability for a long period when filled into a container alone without any restrictions other than the container. Further, depending upon kinds of the material of the container, there is the problem that vitamin As are transferred to the container and the contents of vitamin As in the inner solution decrease drastically. Therefore, it was almost impossible to obtain a highly practical aqueous eye drop solubilizing vitamin As.

[0003]

[Problems to be Solved by the Invention] The objective of the present invention is to maintain vitamin As stably for a long practical period in an aqueous eye drop containing vitamin As solubilized using a nonionic surfactant.

[0004]

[Means for Solving the Problems] The aqueous eye drop solubilizing vitamin As in the present invention is characterized in that the inner solution is filled into a polyethylene terephthalate container capable of shielding a wavelength of 380nm or less by adding a pigment or pigments and U-polymer.

[0005]

[Mode of Carrying out the Invention] Vitamin As that are an essential component of the present invention include vitamin A itself as well as a vitamin A-containing mixture such as vitamin A oil and the like, and

vitamin A derivatives such as vitamin A fatty acid esters and the like. Specifically, retinol palmitate by Japan Roche Corporation 1,700,000 (I.U. International Unit) is known. Vitamin As can generally be mixed into an eye drop composition at a ratio ranging from 0.003 to 0.1 wt%, and preferably ranging from 0.01 to 0.05 wt%. In addition, an applicable range of international units of vitamin A ranges from 1 to 100,000 units, but is not limited by this.

[0006] As a nonionic surfactant that is the second essential component of the present invention, higher fatty acid esters such as water-soluble polyoxyethylene hardened castor oil, polyoxyethylene sorbitan higher fatty acid esters and sucrose fatty acid esters are available. For example, polyoxyethylene (p=60) hardened castor oil, polyoxyethylene (p=20) sorbitanmonooleate are available. In this case, p represents the mean number of the added mols of ethylene oxide. Specifically, Nicol HCO-40, HCO-50, HCO-60, TO-10 and the like by Nikko Chemicals Co., Ltd. can be used. The nonionic surfactant can generally be added as a ratio of 0.01 to 1.0 wt%, and preferably in a range from 0.05 to 0.2 wt%, in the eye drop composition.

[0007] As for the polyethylene terephthalate, which is the third essential component in the present invention, those which can be formed as a container can be used regardless of grades and etc. Specifically, RT543 by Japan Unipet Co., Ltd. can be used. If the main material of the container is something other than polyethylene terephthalate, transfer of vitamin As to the container material tends to occur easily, so the content of vitamin As in the inner solution decreases.

[0008] As for a pigment, which is the fourth essential component in the present invention, a material which can be blended well with the container material polyethylene terephthalate and exhibits high light shielding is desirable. For example, Tinuvin, yellow dyes of the anthraquinone series, yellow dyes of the monoazo series, cyanine blue, iron oxide, zinc oxide, titanium oxide and the like can be listed. A pigment can be generally added at a ratio ranging from 0.1 to 10 wt% relative to the polyethylene terephthalate, but it is not always limited to this range. If a pigment is not added at all, or in the case when the light shielding wavelength of the container is less than 380 nm even though a pigment is added, if it is used practically for a long time and only this container is used, the contents of vitamin As in the inner solution decrease significantly.

[0009] As for a U-polymer, which is the fifth essential component in the present invention, a non-crystalline polyarylate consisting of an aromatic dicarboxylic acid and dihydric phenol can be used. As the U-polymer of the present invention, one that can be blended with polyethylene terephthalate as the main material of the container is desirable. Specifically, U-100 and U-1060 by Unitica Co., Ltd. can be used. A U-polymer is added generally at a ratio ranging from 1 to 20 wt% relative to polyethylene terephthalate, but it is not limited by this. Vitamin As in the inner solution can be further stabilized by adding both a U-polymer and a pigment.

[0010] If desirable, the following other compounds can be added to the aqueous eye drop solubilizing vitamin As in the present invention:

other vitamins; chemical agents such as dipotassium glycyrrhizinate, zinc sulfate, sulfamethoxazole, allantoin, lysozyme chloride and the like; antiseptics such as benzalkonium chloride, benzethonium chloride, chlorhexidine gluconate, sorbic acid, chlorobutanol and the like; sugars such as mannitol, sorbitol and the like; isotonic agents such as potassium chloride, sodium chloride, propylene glycol and the like; buffering agents such as citric acid, boric acid, sodium hydrogen phosphate, glacial acetic acid and the like; and fragrance such as 1-menthol and the like.

[0011] The method of preparation of an aqueous eye drop solubilizing vitamin As in the present invention is not particularly specified. For example, vitamin A acetate is solubilized in water using polyoxyethylene hardened castor oil. Subsequently, an agent such as panthenol is added to be dissolved and a buffering agent is added to adjust pH. It is filled into a polyethylene terephthalate container blocking a wavelength of 380 nm or less. As a result, when it is left in a container for a long time, an aqueous eye drop solubilizing vitamin As which is stable in light can be obtained and the inner solution does not permeate into the container.

[0012] The aqueous eye drop solubilizing vitamin As in the present invention has a desirable pH ranging from 3.0 to 9.0, and more preferably from 5.0 to 8.5. If the pH of the eye drop exceeds the upper limit, the effect of stabilizing vitamin As is reduced.

[0013]

[Effects of the Invention] According to the present invention where in an aqueous eye drop solubilizing vitamin As is provided, in the aqueous dye drop solubilizing vitamin As using a nonionic surfactant, if it is

filled into a container made of polyethylene terephthalate blocking a wavelength of 380 nm or less with the addition of a pigment or pigments and U-polymer, decomposition of vitamin As in light can be prevented and the inner solution does not permeate into the container, even if it is stored in a container alone for a long period.

[0014]

[Embodiments] Embodiments 1 through 4 and Comparative Examples 1 through 6

Eye drops with the prescriptions shown in Tables 1 and 2 were prepared and filled into a container blocking a variety of wavelengths. The samples were exposed under a white fluorescent lamp (1,000 Lux) for 2 weeks. The containers were placed laterally and stored such that eye drops could be efficiently irradiated by the fluorescent lamp. The remaining rates of vitamin A palmitate were measured and the results are shown in the same table. The eye drop was adjusted to pH 6.0 by adding sodium dihydrogen phosphate and disodium hydrogen phosphate, and its osmotic pressure was respectively adjusted to 290mOsm by sodium chloride. The residual rates of vitamin A palmitate in the eye drop were measured by high speed liquid chromatography. The vitamin A palmitate content was measured immediately after production and storage, and calculated using Equation-1. The shielding wavelength of the container was measured as follows. A plate of the container material was prepared with a thickness of approximately 1 mm. Then, its transmission rate was measured using a spectrophotometer. When the transmission rate was 10% or less, that was determined as the range of wavelength shielding.

Equation-1

$$a)\text{ビタミンA類(VA)残存率(\%)} = \frac{b)\text{保存後のVA含量}}{c)\text{製造直後のVA含量}} \times 100$$

Key: a)Residual rate of vitamin A (VA)(%); b)VA content after storage; c)VA content immediately after production)

[0015]

[Table 1]

| 配合量 (g/100ml) | 実施例 1 | 実施例 2 | 比較例 1 | 比較例 2 | 比較例 3 |
|---|---|---|---|---|---|
| ﾋﾞﾀﾐﾝA酢酸ｴｽﾃﾙ | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 |
| ﾎﾟﾘｵｷｼｴﾁﾚﾝ(20)ｿﾙﾋﾞﾀﾝﾓﾉｵﾚｰﾄ | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 |
| 10%塩化ベンザルコニウム液 | 0.05 | 0.05 | 0.05 | 0.05 | 0.05 |
| 精製水 | 適量 | 適量 | 適量 | 適量 | 適量 |
| 容器材質<br>顔料<br>遮光波長 (nm) | PET<br>○<br>390<br>以下 | PET<br>○<br>400<br>以下 | PET<br>×<br>380<br>以下 | PET<br>○<br>330<br>以下 | PET<br>○<br>360<br>以下 |
| ﾋﾞﾀﾐﾝA酢酸ｴｽﾃﾙ含有率 (%) | 89 | 99 | 0 | 28 | 68 |

略号　容器材質：PET　ポリエチレンテレフタレート

凡例　顔　料：○ 添加　× 無添加

[Translator's note: please refer to the original description]

Key:

| Amounts mixed (g/100ml) | Embodiment 1 | Embodiment 2 | Comparative Example 1 | Comparative Example 2 | Comparative Example 3 |
|---|---|---|---|---|---|
| Vitamin A palmitate | | | | | |
| Polyoxyethylene (20) sorbitan monooleate | | | | | |
| 10% benzalkonium chloride solution | | | | | |
| Distilled water | Appropriate amount | Appropriate amount | Appropriate amount | Appropriate amount | Appropriate amount |
| Container material | PET | PET | PET | PET | PET |
| Pigments | ○ | ○ | X | ○ | ○ |
| Shielding wavelength (nm) | 380 or less | 450 or less | 300 or less | 330 or less | 360 or less |
| Vitamin A palmitate content (%) | | | | | |

Abbreviations: Container material: PET polyethylene terephthalate

Legend Pigment: ○ Added × Not added

[0016]

[Table 2]

| 配合量（g/100ml） | 実施例3 | 実施例4 | 比較例4 | 比較例5 | 比較例6 |
|---|---|---|---|---|---|
| ビタミンAパルミテート | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 |
| ポリオキシエチレン(20)ソルビタンモノオレート | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 |
| 10%塩化ベンザルコニウム液 | 0.05 | 0.05 | 0.05 | 0.05 | 0.05 |
| 基剤水 | 適量 | 適量 | 適量 | 適量 | 適量 |
| 容器材質 | PET | PET | PET | PC | PP |
| 顔料 | ○ | ○ | × | ○ | ○ |
| U－ポリマー | ○ | ○ | ○ | ○ | ○ |
| 遮光波長（nm） | 380以下 | 450以下 | 320以下 | 400以下 | 430以下 |
| ビタミンAパルミテート含有率（%） | 34 | 100 | 25 | 55 | 64 |

略号　容器材質：PET　ポリエチレンテレフタレート

PC　ポリカーボネート

PP　ポリプロピレン

凡例　顔　料：○　添加　×　無添加

U－ポリマー：○　添加　×　無添加

[Translator's note: please refer to the original description]

Key:

| Amounts mixed (g/100ml) | Embodiment 3 | Embodiment 4 | Comparative Example 4 | Comparative Example 5 | Comparative Example 6 |
|---|---|---|---|---|---|
| Vitamin A palmitate | | | | | |
| Polyoxyethylene (20) sorbitan monooleate | | | | | |
| 10% benzalkonium chloride solution | | | | | |
| Distilled water | Appropriate amount | Appropriate amount | Appropriate amount | Appropriate amount | Appropriate amount |
| Container material | PET | PET | PET | PC | PP |
| Pigments | ○ | ○ | X | ○ | ○ |
| U-polymer | ○ | ○ | ○ | ○ | ○ |
| Shielding wavelength (nm) | 380 or less | 450 or less | 320 or less | 400 or less | 400 or less |
| Vitamin A palmitate content (%) | | | | | |

Abbreviations: Container material: PET Polyethylene terephthalate
PC Polycarbonate
PP Polypropylene

Legend Pigment: ○ Added × Not added
U-polymer: ○ Added × Not added

[0017] Embodiment 5

2 g polyoxyethylene (60) hardened castor oil (Nikol HCO-60) and 0.4 g vitamin A palmitate (1,700,000 I.U.) were dissolved by heating. This was mixed with 0.5 g tetrahydrozoline chloride, 0.1 g benzethonium chloride, 0.05 g 1-menthol, 5 g propylene glycol, 1 g arantoin, 0.2 g panthenol, 10 g epsilon-aminocapronic acid and 0.05 g disodium ethylenediamine tetraacetate. After the pH was adjusted to 7.0 by adding sodium hydroxide, the total amount was adjusted to 1000ml by adding purified water. After sterilized filtration, the mixture was filled into a polyethylene terephthalate eye drop container blocking wavelengths of 380nm or less in which a pigment was added to prepare an eye drop. This agent was stored under a white fluorescent lamp (1000Lux) for 2 weeks,

and the vitamin A palmitate residual rate was found to be 89%, which was relatively high.

[0018] Embodiment 6

2 g polyoxyethylene (50) hardened castor oil (Nikol HCO-60) and 0.4 g vitamin A palmitate (1,700,000 I.U.) were dissolved by heating. This was mixed with 0.5 g tetrahydrozoline chloride, 0.1 g benzetonium chloride, 0.05 g 1-menthol, 5 g propylene glycol, 1 g arantoin, 0.2 g panthenol, 10 g epsilon-aminocapronic acid and 0.05 g disodium ethylenediamine tetraacetate. After the pH was adjusted to 5.5 by adding diluted hydrochloric acid, the total amount was adjusted to 1000ml by adding purified water. After sterilized filtration, the mixture was filled into a polyethylene terephthalate eye drop container blocking wavelengths of 380nm or less in which U-polymer was added to prepare an eye drop. This agent was stored under a white fluorescent lamp (1000Lux) for 2 weeks, and the vitamin A palmitate residual rate was found to be 93%, which was relatively high.

[0019] Embodiment 7

1.5 g polyoxyethylene (40) hardened castor oil (Nikol HCO-60), 0.5 g vitamin E acetate and 0.2 g vitamin A palmitate (1,700,000 I.U.) were dissolved by heating. This was mixed with 0.5 g tetrahydrozoline chloride, 0.1 g benzetonium chloride, 0.05 g 1-menthol, 5 g propylene glycol, 1 g arantoin, 0.2 g panthenol, 10 g epsilon-aminocapronic acid and 0.05 g disodium ethylenediamine tetraacetate. After the pH was adjusted to 5.5 by adding diluted hydrochloric acid, the total amount was adjusted to 1000ml by adding purified water. After sterilized filtration, the

mixture was filled into a polyethylene terephthalate eye drop container blocking wavelengths of 380nm or less in which pigments were added to prepare an eye drop. This agent was stored under a white fluorescent lamp (1000Lux) for 2 weeks, and the vitamin A palmitate residual rate was found to be 91%, which was relatively high.

[0020] Embodiment 8

1.5 g polyoxyethylene (20) hardened castor oil (Nikol TO-10), 0.5 g vitamin E acetate and 0.2 g vitamin A palmitate (1,700,000 I.U.) were dissolved by heating. This was mixed with 0.5 g tetrahydrozoline chloride, 0.1 g benzetonium chloride, 0.05 g 1-menthol, 5 g propylene glycol, 1 g arantoin, 0.2 g panthenol, 10 g epsilon-aminocapronic acid and 0.05 g disodium ethylenediamine tetraacetate. After the pH was adjusted to 7.0 by adding sodium hydroxide, the total amount was adjusted to 1000ml by adding purified water. After sterilized filtration, the mixture was filled into a polyethylene terephthalate eye drop container blocking wavelengths of 380nm or less in which U-polymer was added to prepare an eye drop. This agent was stored under a white fluorescent lamp (1000Lux) for 2 weeks, and the vitamin A palmitate residual rate was found to be 95%, which was relatively high.